2019

Does Sertraline Decrease Depression In Patients Who Suffered A Traumatic Brain Injury (TBI)?

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Does Sertraline Decrease Depression In Patients Who Suffered A Traumatic Brain Injury (TBI)?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 14, 2018

ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not "Does sertraline decrease depression in patients who suffered a traumatic brain injury (TBI)?"

STUDY DESIGN: Review of three randomized controlled trials (RCTs) published in English between 2009-2016.

DATA SOURCES: One RCT and two double-blind, placebo-controlled, RCTs found via PubMed evaluated the benefit of the antidepressant drug, sertraline (Zoloft), in decreasing depression in patients who suffered a TBI.

OUTCOMES MEASURED: Main outcomes were measured using the DSM-IV, Hamilton Rating Score for Depression (HAM-D)[6], Beck Anxiety Inventory (BAI)[6], and the Life-3 quality of life (QOL)[6], Mini-International Neuropsychiatric Interview[7], Patient Health Questionnaire-9 (PHQ-9)[9] and World Health Organization QOL (WHOQOL)[9].

RESULTS: Ashman, Cantor, Gordon, et al.[6] found that 59% of patients receiving sertraline were treatment responders with a NNT=4 x^2=3.1 and p=0.08, making these findings statistically insignificant. Jorge, Acion, Burin et al.[7] reported that the likelihood of post-TBI depression was 4.6 times more likely in the placebo group than in the group receiving sertraline with a NNT=6, NNTB=4, and the NNH=73, (p=0.03). Ansari, Jain, Sharma et al.[9] recorded an improvement of 9.55 in mean PHQ-9 scores from baseline (p= 0.04) and a 16.3-22.1% improvement in mean WHOQOL scores from baseline in the group receiving sertraline, with statistically significant differences in WHOQOL domains 1-3.

CONCLUSIONS: There was evidence in all 3 studies to support the benefits of sertraline in decreasing post-TBI depression. However, only two studies provided statistically significant data. Based on the findings in the two studies that reported data with statistical significance, sertraline does decrease depression in patients who suffered a TBI. More specifically, there is also significant evidence that supports the prophylactic use of sertraline to prevent post-TBI depression.

KEY WORDS: Traumatic Brain Injury, Sertraline

INTRODUCTION

Depression is a mood disorder characterized by a depressed mood or a loss of interest in activities that one used to enjoy (anhedonia), which is often accompanied by feelings of guilt, a change in sleep, weight, energy, cognition, concentration, psychomotor behavior, and homicidal or suicidal ideation.[1] A multitude of biopsychosocial and genetic factors have been found to a play a role in the etiology of depression such as trauma, family history, substance abuse, divorce, pregnancy, and certain medications. Additionally, correlations exist between depression and chronic medical conditions such as multiple sclerosis, rheumatoid arthritis, cardiovascular disease, cerebrovascular disease, and traumatic brain injury (TBI).[1]

A TBI is defined as, "an alteration in brain function, or other evidence of brain pathology, caused by an external force"[2]. This injury may be due to any direct or indirect, angular or rotational force to the head or neck that is powerful enough to cause shear stress on brain tissue and blood vessels.[3] It is unknown what exact pathological changes produced by a TBI directly cause depressive symptoms, however, it is known that a TBI causes alterations in brain functioning due to biochemical cascades leading to cell death. A forceful injury to the head can cause cellular strain and deformation of brain tissue leading to two molecular responses. One is the release of the neurotransmitter glutamate, which increases intracellular calcium leading to cytotoxicity and cell death.[2] Second, is a change in the ionic equilibrium in neuronal cell membranes. Either cellular response can lead to immediate cell death or, over time, the neuron may repair itself.[2] Since there is no way to predict which cells will die or regenerate, defining the severity or prognosis of a TBI is challenging, however, knowing the mechanism of injury is useful. In determining which regions of the brain were most likely damaged based on the directional forces, there can be potential relationships drawn between the pathology and

symptomology. For example, orbital-frontal brain damage has been linked to irritability, frontal regions to impulsivity, and frontal and temporo-limbic regions to depression.[2]

The pathophysiology of depression is not well understood but has been attributed to an alteration in neurotransmitters such as serotonin, histamine, dopamine, norepinephrine, and epinephrine. Alterations in neuroendocrine functioning have also been linked to depression such as increased levels of cortisol and corticotropin-releasing hormone (CRH), as well as a decreased response of thyroid stimulating hormone (TSH) to thyroid releasing hormone (TRH).[4] The widespread etiology and complex pathophysiology behind depression is what makes treating this disorder challenging.

The gold standard treatment for depression is the class of medications known as selective serotonin reuptake inhibitors (SSRIs), such as sertraline, paroxetine, and fluoxetine. Other medication classes such as SNRIs, NRDIs, NaSSAs, TCAs, and MAOIs are also used, as well as psychotherapy, electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS).[1] Most often, treatment modalities consist of a combination of the therapies described above. Common treatments for a TBI include pain relievers (naproxen, ibuprofen, acetaminophen etc.), strict restriction of activity/stressors (exercise, reading, school, work, loud noises, bright lights, social/family stressors), and also vitamins such as melatonin, B12, and fish oil.[3]

A range of 6-77% of those who experience a TBI go on to suffer from depressive disorders.[5] Within this range, 25-50% will suffer post-TBI depression within the first year and 26-64% of these patients will suffer from lifetime depression.[5] Post-TBI depression has been correlated to functional disability, decreased participation in activities of daily living, sexual dysfunction, lower ratings of health and QOL, reduced employment, and increased rates of suicidal ideation.[6] There is an estimated 2.5 million to 6.5 million people who suffer from a

disability post-TBI, which is associated with an estimated total annual cost of $60 billion.[7] The yearly incidence of TBIs in the US is about 1.7 million[7], but in the past 5 years, annual rates for TBI-related ER visits, hospitalizations, and deaths have been recorded as high as 2.8 million.[8]

About 30% of patients seen by their primary care physicians report depressive symptoms.[1] It is important to know if these symptoms are related to a TBI because it will change patient management. Using sertraline for post-TBI depression is efficacious due to the drugs specific mechanism of action. As previously mentioned, TBIs cause neuronal damage and cell death, which results in alterations in cellular communication pathways and neuronal release, with the potential of decreasing normal serotonin levels. Sertraline inhibits the reuptake of serotonin by presynaptic neurons, which increases the amount of serotonin in the brain.

Physician assistants (PAs) play a vital role in assessing and treating psychological illness. Post-TBI depression is relevant to patients and the PA practice because it is a prevalent cause of morbidity and mortality. Improvements in patient QOL and healthier outcomes can be achieved by implementing the use of sertraline for the treatment or prevention of post-TBI depression.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not "Does sertraline decrease depression in patients who suffered a traumatic brain injury (TBI)?"

METHODS

One RCT and two double-blind, placebo-controlled, RCTs were found via PubMed using specific inclusion criteria for this review. The patient population is patients 18 years and older who suffered a TBI. The intervention studied was oral sertraline. The control group used for comparison were patients 18 years and older who suffered a TBI and did not receive sertraline.

Outcomes measured were improvements in depressive symptoms, QOL, and prevention of depression in patients post-TBI.

DATA SOURCES:

Keywords that were used to search for articles were "traumatic brain injury" and "sertraline". Each article consisted of published data written in the English language. Articles were selected based on their relevance to the clinical question and were required to have patient-oriented evidence that matters (POEMs). The inclusion criteria for articles used in this review were as follows: RCTs with outcomes that were POEMs, published after 2009, participants above the age of 18 who suffered a TBI, the use of PO sertraline as an intervention. Studies that were excluded from this review were studies that were not RCTs, studies without POEMs, published before 2009, used patients under the age of 18, and who used patients who did not meet criteria for a TBI. Statistics reported included the following: p-value, mean ($\bar{x}$), standard deviation (SD), chi-square (x^2), odds ratio (OR), F-statistic (F), confidence interval (CI), relative benefit increase (RBI), absolute benefit increase (ABI), numbers needed to treat (NNT), numbers needed to treat to benefit (NNTB), and numbers needed to harm (NNH). See Table 1 for demographics and inclusion/exclusion criteria for the articles used in this review.

OUTCOMES MEASURED

The outcomes measured in all of the studies were POEMs. Ashman, Cantor, Gordon et al.[6] measured the efficacy of sertraline in the treatment of post-TBI depression using the HAM-D, BAI, and Life-3 QOL. Jorge, Acion, Burin et al.[7] measured the time to onset and the prevention of depressive disorders post-TBI using the Mini-International Neuropsychiatric Interview and DSM-IV criteria. Ansari, Jain, Sharma et al.[9] measured the treatment of depression and improvements in QOL using the PHQ-9 and WHOQOL questionnaire.

Table 1: Demographics and Characteristics of Articles Reviewed

Study	Type	#Pts	Age	Inclusion	Exclusion	W/D	Intervention
Ashman[6] (2009)	RCT, double blind	52	18+	18 years or older, hx of TBI with a documented LOC/ evidence of a TBI (ie, pathology on neuroimaging); At least 6 months post-injury; dx criteria for a major depressive episode (DSM-IV); score 18 or greater on the HAM-D; Be able to comprehend or answer verbal/written questionnaires	Suspected to be using antidepressant medication; Currently in psychotherapy; have active suicidal plans or depression severe enough to require hospitalization; have a serious medical illness; pregnant or breast-feeding; mass brain lesions or other neurologic diagnoses other than TBI; history of current or past psychosis or mania using DSM-IV criteria; current substance abuse disorder using DSM-IV criteria; history of clinically significant liver or renal disease.	11	Sertraline PO qd x10w; 25mg QD x 2w; adjusted @ end of week 2 & q2 weeks after Range of 25 to 200mg/d depending on clinical response and tolerance by the end of the clinical trial
Jorge[7] (2016)	RCT, double blind	94	18-85	Met Center for Disease Control (CDC) criteria for TBI; Mild, Moderate, or Severe TBI as categorized by initial Glasgow Coma Scale (GCS) scores; Complete recovery from Post Traumatic Amnesia (PTA) within 4 weeks of the traumatic episode.	Penetrating head injuries; Clinical or neuro-radiological evidence of spinal cord injury; severe comprehension deficits; previous cognitive decline consistent with dementia; DSM-IV mood, anxiety or psychotic disorder (pts with a hx of alcohol abuse or alcohol dependence during the year preceding TBI are still included in the study); PO antidepressants at the time of TBI or 6 month period prior to; failed a previous trial of sertraline/ SE that prompted the drug to be d/c; Pregnancy; plan to become pregnant; Severe complicating illness such as neoplastic ds or uncompensated heart, renal or liver failure.	15	Sertraline, 25 mg, PO, QD x 5 days 50 mg, PO QD x 5d 100 mg, PO, QD x the remainder of the 24-week trial/until development of mood disorder
Ansari[9] (2014)	RCT	89	18+	Male pts 18 years or older with a hx of TBI with a documented LOC or other evidence of a TBI (determined by pathology on neuroimaging); comprehend or answer verbal/written questionnaires; 2-week old injury	Females, Dx of a serious medical illness, substance abuse disorder (DSM-IV); Men with a mass lesions or other neurologic dx other than TBI; Men who have a hx of current or past psychosis or mania, major depressive disorder (MDD) or any other mental disorder except current depression, clinically significant liver or renal ds.	9	Sertraline, 50mg PO QD x 24 weeks

RESULTS

Ashman, Cantor, Gordon, et al[6] conducted a double-blind RCT to study the efficacy of sertraline in the treatment of post-TBI depression. Their study consisted of 52 participants with a mild, moderate, or severe TBI, a diagnosis of major depression disorder (MDD), and a baseline

HAM-D score of 18 or greater. The study was conducted at a research center where physicians visited participants every 2 weeks to collect data in the form of HAM-D, Life-3, and BAI questionnaires. Response to treatment was determined by a reduction of a HAM-D score by 50%. In the experimental group, 59% were considered treatment responders, while only 32% in the control group with a x^2 value of 3.1 and a p-value of 0.08.[6] The NNT in this study was 4. These results are further illustrated in Table 2.

Table 2. Treatment Responders Using HAM-D Scores[6]

CER	EER	RBI	ABI	NNT
32%	59%	84.4%	27%	3.7 (4)

CER= Control Event Rate; EER= Experimental Event Rate; RBI= Relative Benefit Increase; ABI= Absolute Benefit Increase

The experimental group showed decreased BAI scores and increased Life-3 scores after the 10-week trial with mean change from baseline scores of 12.1 and 3.5 respectively, but when compared to control groups these changes were not significant ($p > 0.05$).[6] Out of the 52 participants who started the study, 11 dropped out, 3 of which were removed for clinical reasons. One participant in the treatment group was removed due to increased depression. In the placebo group, two were removed due to increased anxiety and a mild allergic reaction. The other 8 were noncompliant. The intent to treat analysis found significant differences between the last HAM-D score of dropouts and the HAM-D scores of those who remained, with dropouts having higher HAM-D scores with an F-score of 4.0 and p-value of 0.05.[6] There were no adverse events (AEs) or comments on safety/tolerability reported in the 41 participants who completed the study.

Jorge, Acion, Burin et al[7] conducted a double-blind RCT using 94 patients who had suffered a mild, moderate, or severe TBI to determine the efficacy of preventing the onset of a depressive disorder using sertraline. Patients with ongoing depression were excluded from the study and participants with a history of mood disorders were required to be in remission for at least 1 year. Patients were evaluated in person at weeks 2, 4, 8, 12, 16, 20, and 24-weeks and via telephone interviews at 6, 10, 14, 18, and 22-weeks. Out of the 94 patients, 48 received sertraline

and the rest received a placebo. The dosing regime of sertraline can be found in Table 1. The diagnosis of depression was made by experienced psychiatrists using the Mini-International Neuropsychiatric Interview and DSM-IV criteria. After 24-weeks, it was determined that the NNT in order to prevent the onset of a depressive disorder post-TBI using sertraline was 6, the NNTB was 4, and the NNH was 73.[7] The likelihood (x^2) of developing a depressive disorder was 4.6 times higher in the placebo group (p=0.03).[7] These results are organized in Table 3.

Table 3. NNT to Prevent a Depressive Disorder: Risk Comparison[7]

	NNT	NNTB	NNH	95% CI	x^2	p-value
Week 24	5.9 (6)	3.1 (4)	72.1 (73)	3.1-71.1	4.6	0.03

AEs were also considered in this study; however, only two AEs were determined to be higher in the experimental group versus the placebo. The OR for diarrhea was 2.3 (p=0.1) and the OR for dry mouth 7.2 (p=0.01) in the experimental group using a 90% CI. See Table 4.

Table 4. Adverse Events[7]

Adverse Event	Odds Ratio	90% CI	P-value
Diarrhea	2.3	1.0-5.5	0.1
Dry mouth	7.2	1.9-27.6	0.01

Although sexual dysfunction is one of the most common AEs associated with SSRIs, it was determined to be insignificant in this study with a mean and SD of 13.9 and 5.8 in the experimental group and 12 and 3.6, respectively in the placebo group displayed in Table 5.

Table 5. Sexual Dysfunction[7]

	Sertraline	Placebo
ASEX [a] mean (SD)	13.9 (5.8)	12.0 (3.6)

[a] Sexual dysfunction was scaled using the Arizona Sexual Experience Scale (ASEX)

Ansari, Jain, Sharma et al.[9] conducted a RCT on 80 male participants who suffered either a mild or moderate TBI and who were determined to be depressed. This study was carried out in a neurosurgery ward and excluded women to maintain homogeneity among the group. Half of the participants were given sertraline and the control group did not receive a placebo. The mean score and SD of the PHQ-9 at the beginning of the study was 14.88 and 3.6 in the intervention

group and 13.2 and 3.1 in the control group, respectively.[9] At the end of the 24-week study, there was a significant improvement in mean scores in the experimental group compared to the control group with a mean and SD of 5.33 and 2.98 in the experimental and 6.29 and 3.2 in the control group (p=0.04).[9] The mean change from baseline in the experimental group was 9.55, which is considered large for this type of study. This data is organized into Table 6.

Table 6. Improvement in Depression Determined by PHQ-9 Scores[9]

	Sertraline	**Control**
Baseline	14.88 (3.6)[a]	13.2 (3.1)[a]
24 Weeks	5.33 (2.98)[b]	6.29 (3.2)[b]
Mean change from baseline	9.55	6.91

Data recorded as mean (SD); [a] p-value= 0.22; [b] p-value= 0.04

Additionally, improvement in QOL was compared between the experimental and control groups using mean scores of the WHOQOL questionnaire. The WHOQOL uses 4 domains to grade QOL based on physical health (D1), psychological health (D2), social relationships (D3), and environment (D4). There was a significant difference between the mean scores in the experimental group and the control group after 24-weeks in D1-D3. The experimental group showed improvements in mean scores in all 4 domains, while the control group showed a decline in all 4 domains.[9] The percent increase in the mean scores from baseline to the end of the study ranged between 16.3-22.1% for the experimental group.[9] AE and data on safety were not mentioned in this study. See Table 7 below.

Table 7. A Comparison of WHOQOL Scores[9]

	Baseline (x ± SD)	**24 weeks (x ± SD)**	**Mean change from baseline (% increase)**
D1 Sertraline	38.88 ± 11.882[a]	45.38 ± 11.816[e]	6.5 (16.7%)
D1 Control	40 ± 10.997[a]	33.50 ± 12.635[e]	-6.5 (-16.3%)
D2 Sertraline	39.50 ± 14.338[b]	47.23 ± 16.623[f]	7.73 (19.6%)
D2 Control	45.30 ± 14.848[b]	39.13 ± 13.354[f]	-6.17 (-13.6%)
D3 Sertraline	47.60 ± 15.751[c]	58.15 ± 18.565[g]	10.55 (22.1%)
D3 Control	45.95 ± 14.789[c]	40.65 ± 20.202[g]	-5.3 (-11.5%)
D4 Sertraline	37.43 ± 12.683[d]	43.55 ± 13.027[h]	6.13 (16.3%)
D4 Control	44.45 ± 10.261[d]	39.60 ± 11.845[h]	-4.8 (-10.7%)

[a] p= 0.66; [b] p=0.07; [c] p=0.6; [d] p=0.08; [e] *p=0.001;* [f] *p=0.01;* [g] *p=0.001;* [h] p=0.16

DISCUSSION

Two RCTs in this review provided statistically significant data supporting the use of sertraline as an efficacious drug to decrease depression in post-TBI patients. Unfortunately, the study by Ashman, Cantor, Gordon, et al[6] did not produce any statistically significant data; however, their study was limited by the small sample size (n=41) and the short length of time over which the study was conducted (10-weeks). Perhaps if their study were to continue for an additional 14-weeks, similarly to the other 24-weeks long studies, their numbers may have become statistically significant. It should be noted that the main measure used by Ashman, Cantor, Gordon, et al[6] was the HAM-D scale, which is a multidimensional measurement of depressive symptoms that combines 4 subscales to generate one overall score. Some researchers have discounted it as an effective means of determining significant changes in depressive symptoms, especially when a medication is used as the intervention. It is thought that unidimensional subscales are more sensitive predictors of change when analyzed separately.[6]

Ansari, Jain, Sharma et al.[9] found significant improvements in depression and patients QOL based on the PHQ-9 and WHOQOL scale, however, it must be highlighted that this study did not use blinding, only used male participants, and only used patients with mild or moderate TBIs. Therefore, their results cannot be generalized to female patients or those who suffered a severe TBI. Jorge, Acion, Burin et al.[7] used both female and male participants with mild, moderate, and severe TBIs, however 92 of the 94 of the participants were white. Furthermore, only 9 out of 94 of their participants sustained a severe TBI.

In 2014, there were over 837,000 children responsible for TBI-related ER visits, hospitalizations, and deaths in the US[11] and the incidence of sports-related concussions (mild TBI) is estimated between 1.6 to 3.8 million cases annually[3], which makes this a prevalent health

issue for many middle and high school athletes. Since this review only discusses studies with participants over the age of 18, conclusions drawn from this review may not be consistent with the efficacy of this drug in patients who are 17 years old or younger.

Sertraline is a commonly used, inexpensive, and safe drug that has been indicated in the treatment of depression, anxiety, PTSD, OCD, panic disorder, and premenstrual dysphoric disorder. A 25 mg tablet of generic sertraline costs between $2.71 and $2.85 and a 100 mg tablet between $2.84 - $2.92 per tablet.[10] The three studies in this review used daily dosages of sertraline between 25-200 mg, making this a reasonably affordable treatment modality. An additional benefit of this medication is the low side effect profile, although some AE do exist. Some of the more common side effects of this medication are insomnia, dizziness, restlessness, decreased libido, sexual dysfunction, nausea, and diarrhea. It is important to note that a contraindication to this medication is the use of sertraline with other drugs that increase levels of serotonin in the brain such as MAOIs, including linezolid, methylene blue, and sumatriptan.[10] This could lead to "serotonin syndrome" which is a potentially fatal reaction due to an excessive amount of serotonin in the brain leading to hyperthermia, muscle rigidity, alterations in mental status and vital signs. It is especially important to note this drug interaction because sumatriptan is a medication used for migraines, which may be prescribed to a patient post-TBI.

Sertraline does have a "US Boxed Warning" worthy of noting, which states, "Antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adult patients in short-term studies,".[10] Additionally, Beers Criteria considers SSRIs to be "potentially inappropriate medications" for patients over the age of 65 due to their associations with falls and their ability to potentiate the secretion of ADH. Increased levels of ADH can lead

to hyponatremia and, in patients over the age of 65 years old; it is recommended to monitor sodium concentrations when initiating treatment with an SSRI or when changing dosages.[10]

CONCLUSION

Two of the studies in this review provided statistically significant data to support the use of sertraline to decrease depression in patients who suffered a TBI. However, when considering all three studies, evidence is conflicting. This could be due to flaws in the methodology of these studies such as sample size, length of study, and the use of only subjective data in measuring depression. All studies consisted of less than 100 participants and no study lasted longer than 6 months. Future studies should aim to increase sample size, length of intervention, and consider the use of both subjective and objective means of measuring depression such as trending BMI, cognitive function, change in concentration, and change in sleep. Also, the efficacy of sertraline for post-TBI depression in patients under the age of 18 should be considered in future research.

As previously mentioned, no studies investigated if there were significant differences in responses between mild, moderate, or severe TBIs. Also, neither of the three studies sought to identify differences in responses based on the mechanism of the TBI such as motor vehicle accident, assault, or sports-related injuries. Future studies should seek to compare differences in response rates based on severity and mechanism of injury, as well as to compare efficacy based on which region of the brain (frontal, temporal, parietal, occipital) was injured as we know these areas of the brain have specific functions. Additionally, all studies used sertraline alone as the intervention, and it may be useful to identify if any further treatment benefits exist using a multidimensional approach such as sertraline plus behavioral therapy or sertraline with TMS or ECT. This information would be beneficial to patients and PAs regarding educating patients on their prognosis and formulating detailed, efficient, patient-oriented treatment plans.

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